Equilibrium Solubility In Simulated Intestinal Media

Orbito Team – Strathclyde University

WP 1

September 2018

Innovative Tools for Oral Biopharmaceutics

Work Package 1

- Task 1.1 Design of Experiment
- Task 1.3 Design and characterisation of a set of SGIM reflecting the compositions of human GI fluids in the fasted and fed states
- Task 1.4 Optimisation and validation of novel small scale models for dissolution rate and apparent solubility in the designed SGIM
- Task 1.11 Determination of excipient effects on API behaviour in developed in vitro models

Coverage

- Media Parameters
- Basic Experimental Protocol
- Design of Experiment Studies
- Four Component Mixture Design Studies
  - Intestinal Solubility Topography
- Practical Application
  - BCS, Intestinal Solubility Window, PK Prediction
- Experimental Caveats
- Conclusions

Media Parameters

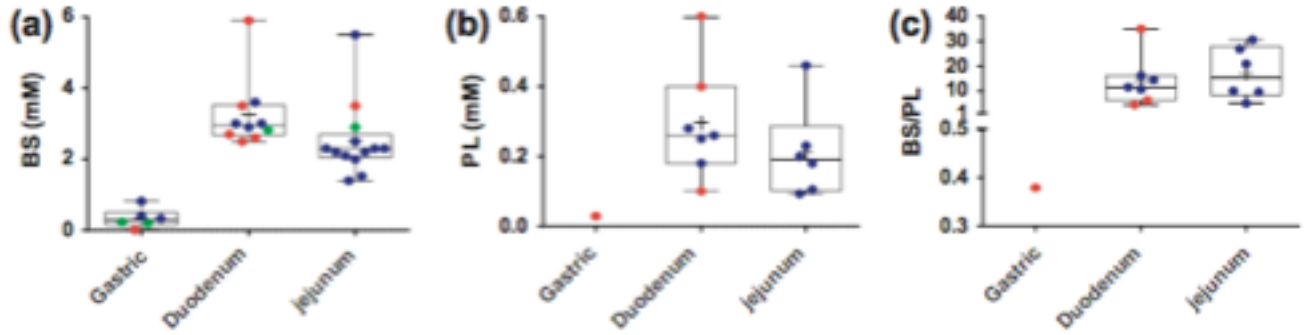
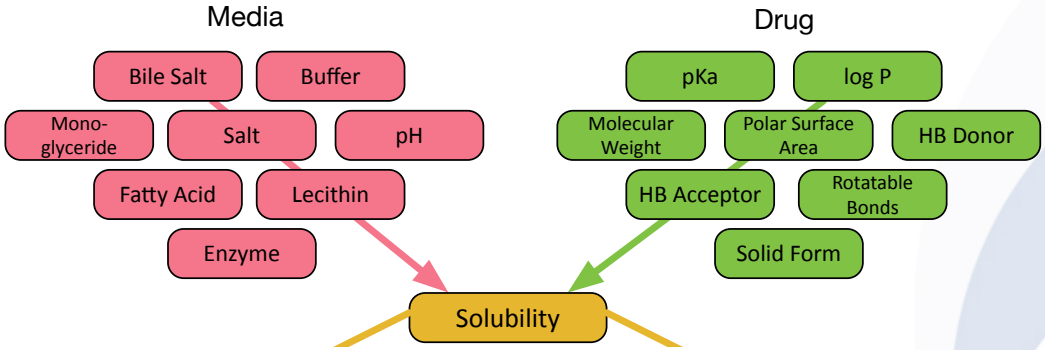
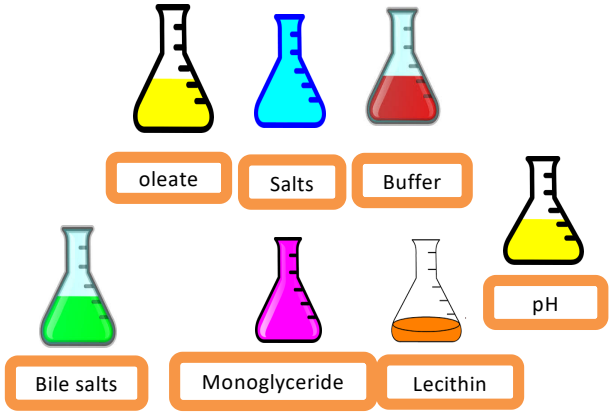


Fig. 4. (a) Bile salt (BS) concentration, (b) phospholipid (PL) concentration, and (c) BS/PL ratio in fasted gastric, duodenal and jejunal fluids. Box–whisker plots show minimum and maximum values, as well as 25, 50 and 75 percentile. The cross indicates the mean value. Each data point represents a group of participants (n = 1–10 colored red, n = 11–20 colored blue and n > 20 colored green) reported in one publication. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Bergstrom et.al., (2014) Eur.J.Pharm.Sci., 57; 173-1999

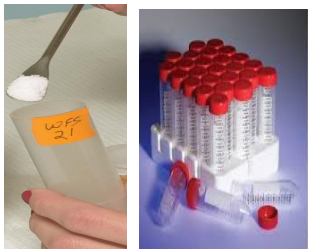


Equilibrium Solubility Measurement



Transferred to centrifuged tube

Drug added



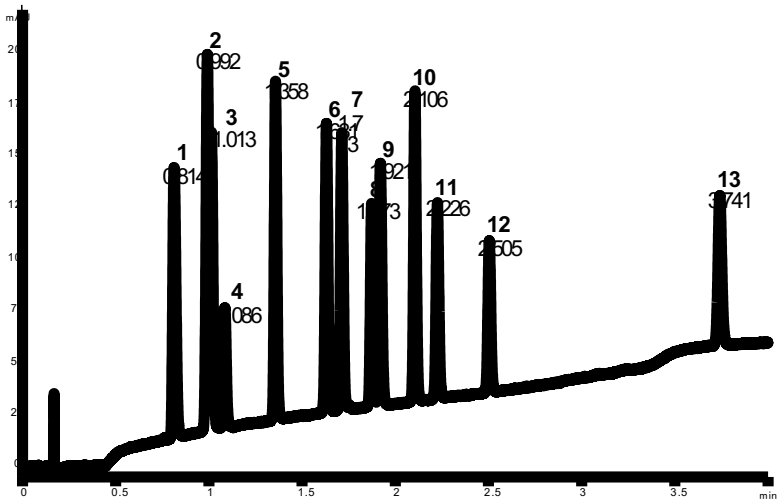
pH adjusted & sample

placed in shaker for one hour

24 hrs @ 37° C

1 ml transferred to Eppendorf tube

Analyzed by HPLC



1: Carvedilol
2: Tadalafil
3: Albendazole
4: Bromocriptine
5: Valsartan
6: Indomethacin
7: Ibuprofen
8: Aprepitant
9: Felodipine
10: Zafirlukast
11: Itraconazole
12: Fenofibrate
13: Probucol

Khadra, I., et.al., (2015) Eur.J.Pharm.Sci., 67; 67-75
Zhou, Z., et.al., (2017) Eur.J.Pharm.Sci., 99; 95-104

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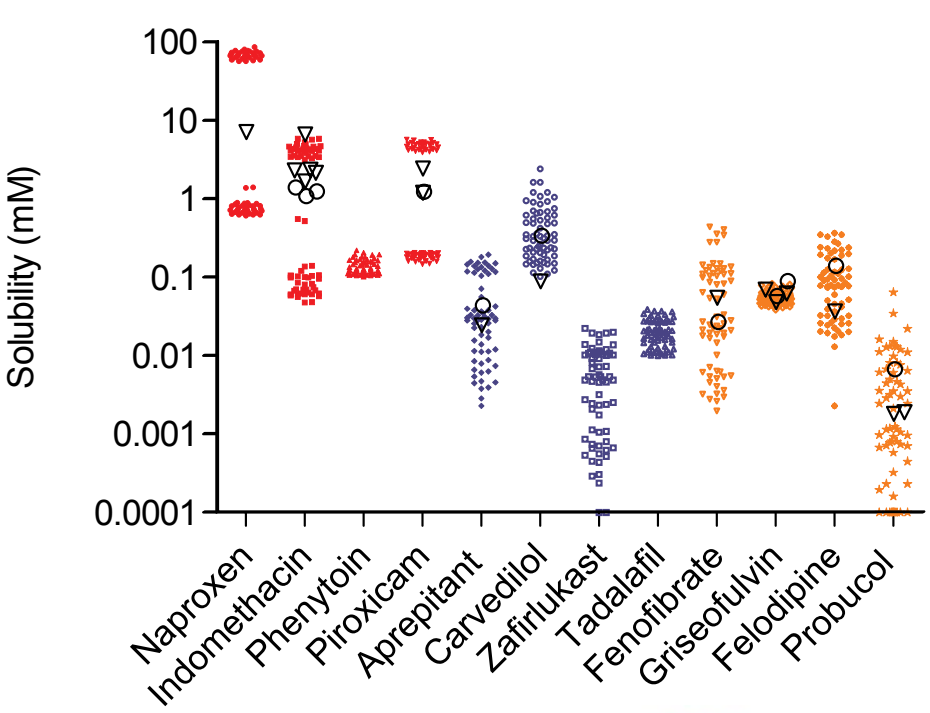
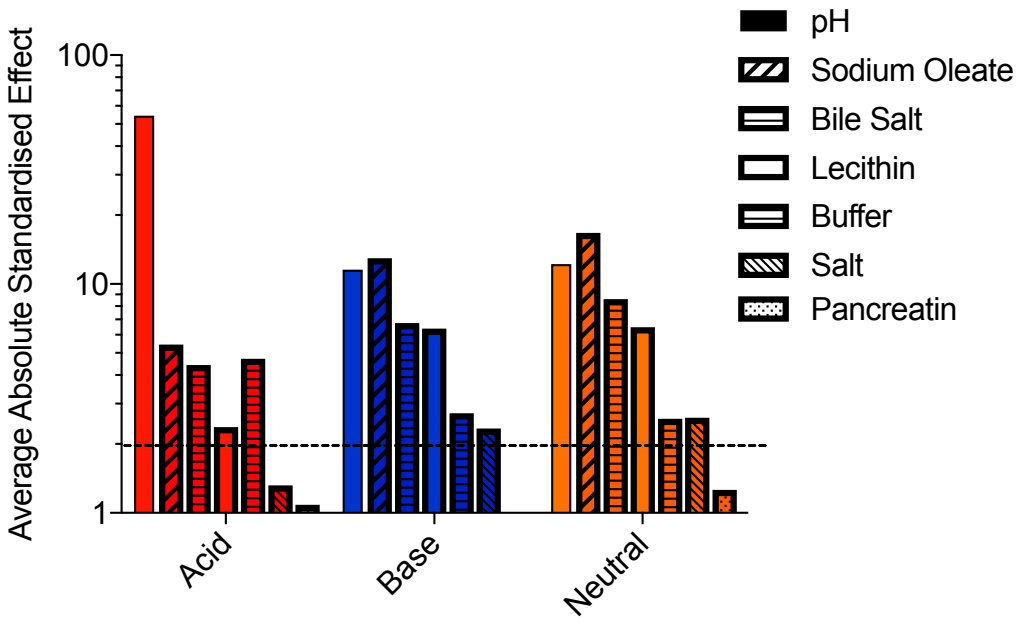
Media Parameters - Design of Experiment

- Fasted
  - Fractional factorial design (quarter)
  - 7 parameters
  - 66 experiments (including duplicates)
- Fed
  - D-optimal design
  - 8 parameters
  - 94 experiments (including duplicates)

Parameter/ Ingredient	Substance	Fasted		Fed		Full Range	
		Lower Limit	Upper limit	Lower Limit	Upper Limit	Lower Limit	Upper Limit
Bile salt (mM)	Sodium TC	1.5	5.9	3.6	24	1.5	24
Lecithin (mM)	Egg PL	0.2	0.75	0.5	4.8	0.2	4.8
Buffer (mM)	NaH2PO4	15	45	-	-	15	45
	Maleic acid	-	-	28.6	58.09	-	-
Salt (mM)	NaCl	68	106	125	203	68	203
pH	NaOH/HCl	5	7	5	7	5	7
Enzyme (U/ml)[1]	Pancreatin	0.5	1	100	150	-	-
Fatty acid (mM)	Sodium oleate	0.5	10	0.8	52	0.5	52
Monoglyceride (mM)	Glyceryl Mono-oleate	-	-	0.5	6.5	0.5	6.5

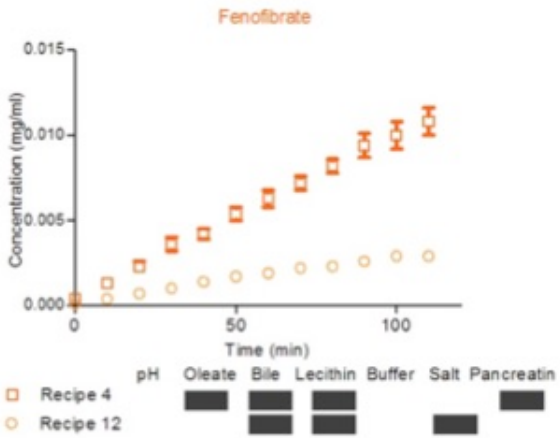
Fasted - Design of Experiment

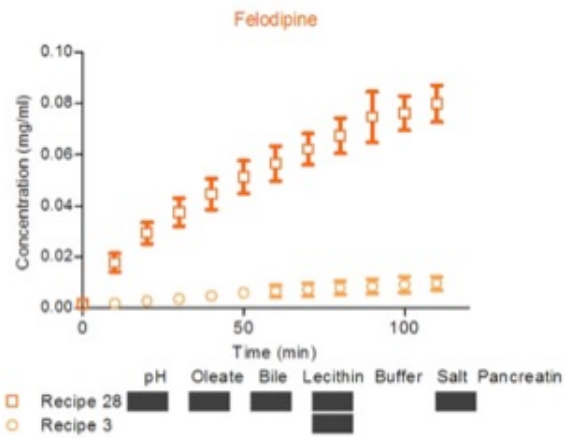




Khadra, I., et.al., (2015) Eur.J.Pharm.Sci., 67; 67-75
See also – Madsen, C., et.al., (2018) Eur.J.Pharm.Sci., 111; 311-319

Unpublished Data





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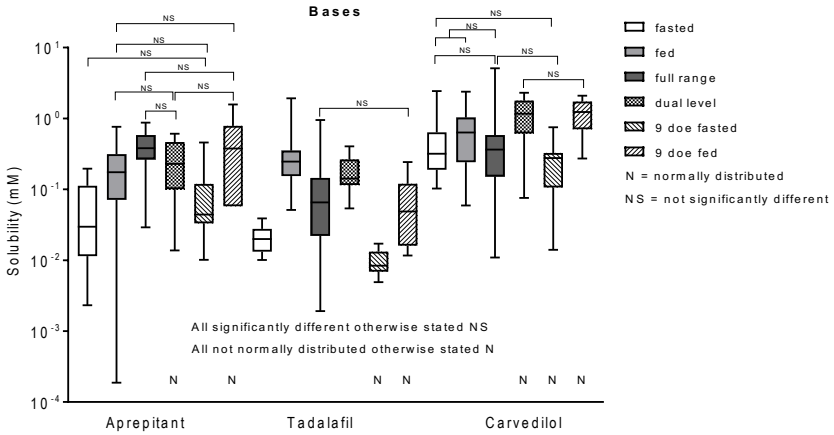
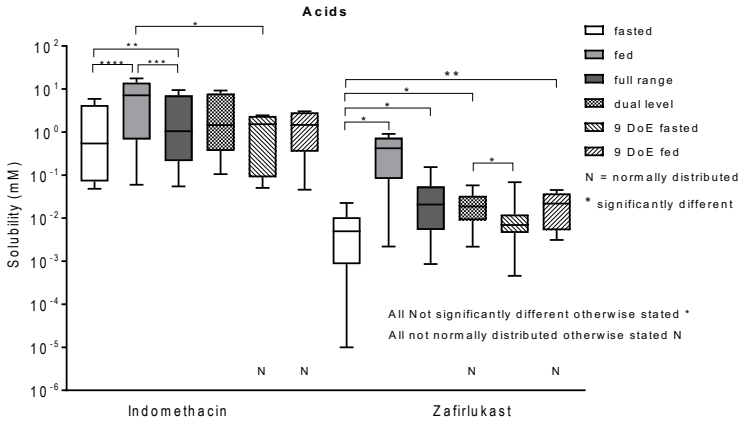
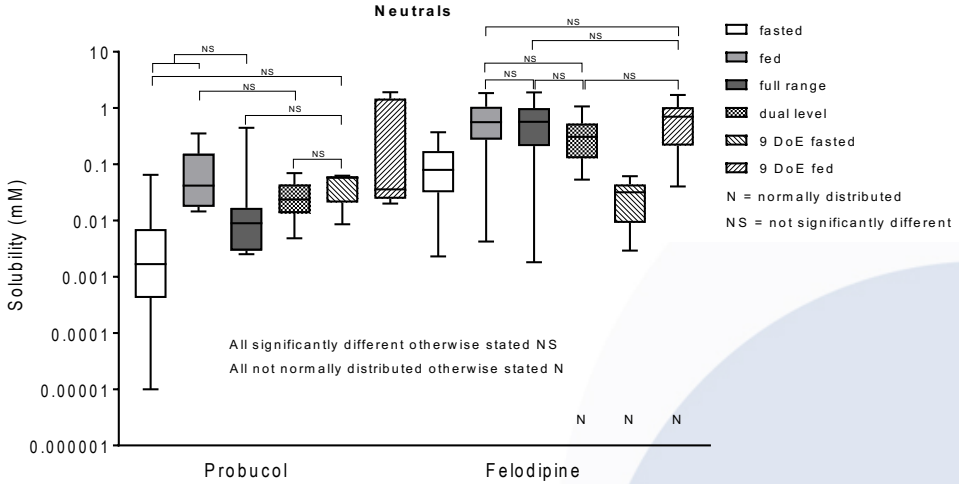
Multiple – Design of Experiment Systems

- Fasted
- Fed
- Combined
- Dual range
- 9 point Fasted and Fed







Khadra, I., et.al., (2015) Eur.J.Pharm.Sci., 67; 67-75
Zhou, Z., et.al., (2017) Eur.J.Pharm.Sci., 99; 95-104
Perrier, J., et.al., (2018) Eur.J.Pharm.Sci., 111; 247-256
Ainousah, B.E., et.al., (2017) Mol.Pharmaceutics 14; 4170-4180
9 Point – unpublished data

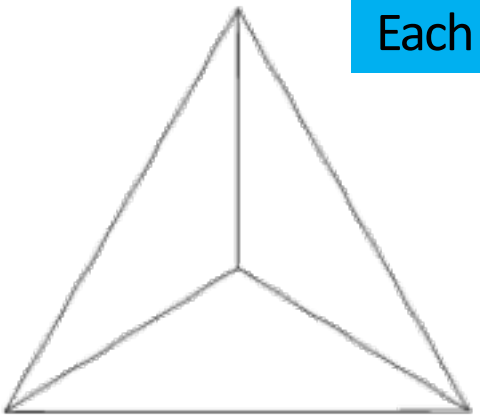
Impact DoE Design on Factor Significance

	Fasted	Fed	Dual Level – Fasted	Dual Level – Fed	9DOE Fasted	9DOE Fed
Indomethacin	pH Bile Salt Buffer Oleate	pH Oleate Bile Salt	pH	pH	pH	pH
Aprepitant	Oleate pH Lecithin	Oleate Bile Salt pH	Oleate Lecithin MG	NS	NS	NS
Tadalafil	Bile Salt pH Buffer Lecithin Oleate Salt	Bile Salt Oleate	NS	NS	pH	NS
Zafirlukast	pH Oleate Bile Salt Lecithin	pH Bile Salt Oleate	pH Cholesterol MG	NS	NS	NS
Carvedilol	Bile Salt Oleate	Bile Salt pH Buffer Oleate	NS	NS	Bile Salt pH	NS
Felodipine	pH Oleate Lecithin Bile Salt	Oleate Bile Salt pH Lecithin	pH Oleate Lecithin MG	Oleate Lecithin Bile Salt MG	Oleate	Bile Salt
Probucol	pH Oleate	Bile Salt MG Oleate Lecithin pH	Oleate BS:PL	Oleate	pH	NS

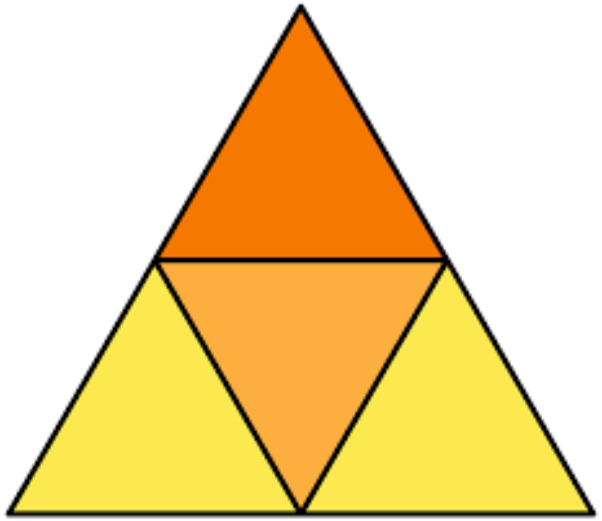
Smaller Design = Lower Factor Resolution

Four Component Mixture Design (4CMD)

- DoE – indicates drug specific behaviour
  - Difficult to visualise
- Four components
  - Bile salt
  - Sodium oleate
  - Lecithin
  - Glyceryl monooleate
- Total amphiphile concentration
  - 11.7 mM
- pH 7.4

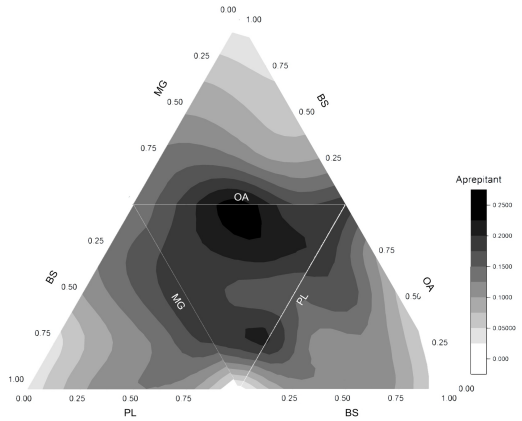


Tetrahedron of solubility
Each Triangle – Ternary Phase Diagram

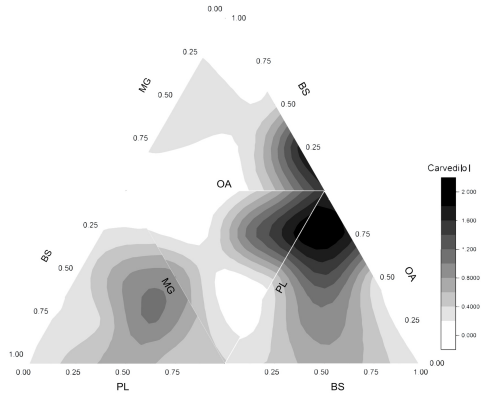


4CMD pH 7.4 TAC 11.7 mM

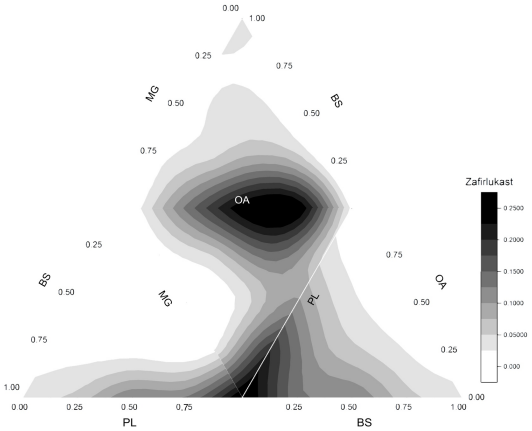
Aprepitant



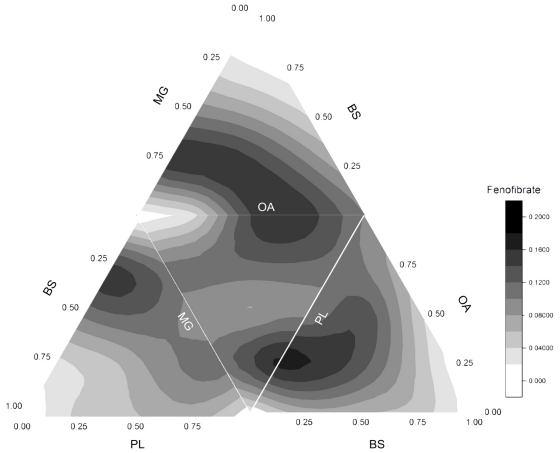
Carvedilol



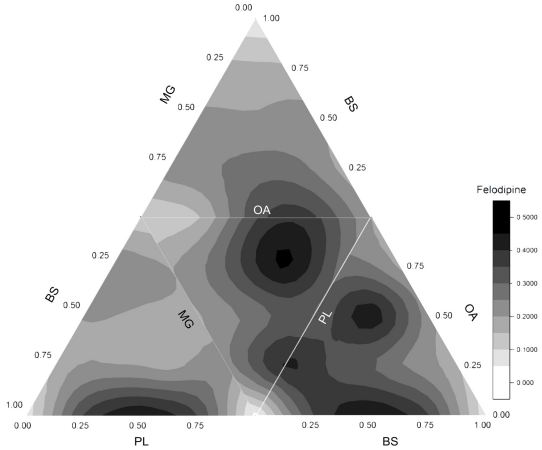
Zafirlukast



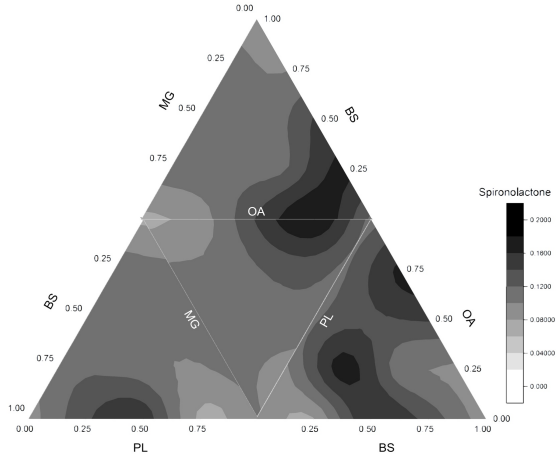
Fenofibrate



Felodipine



Spironolactone



Zhou, Z., et.al., (2017) Mol.Pharmaceutics, 14; 4132-4144

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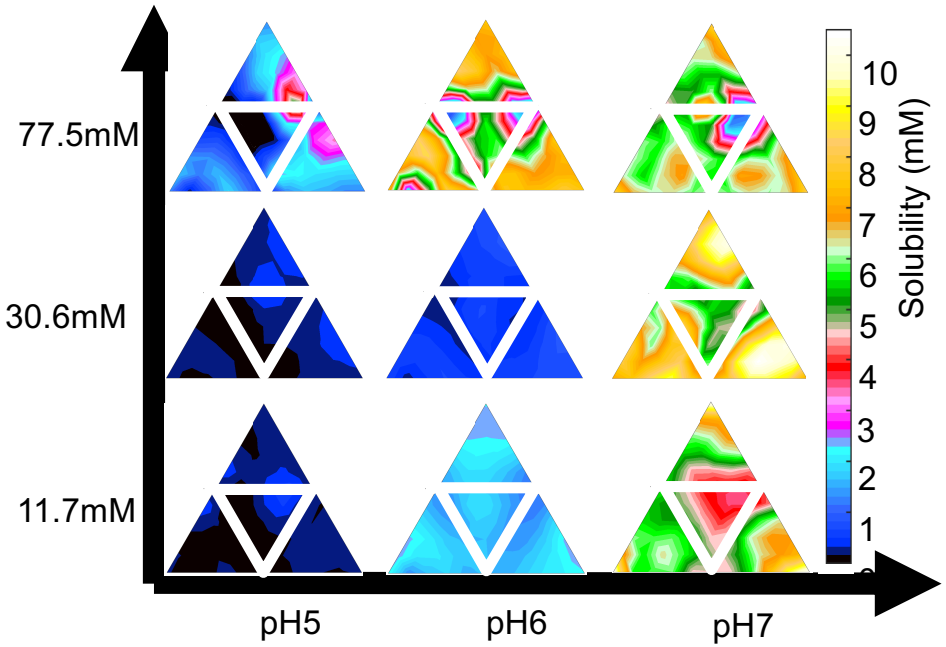
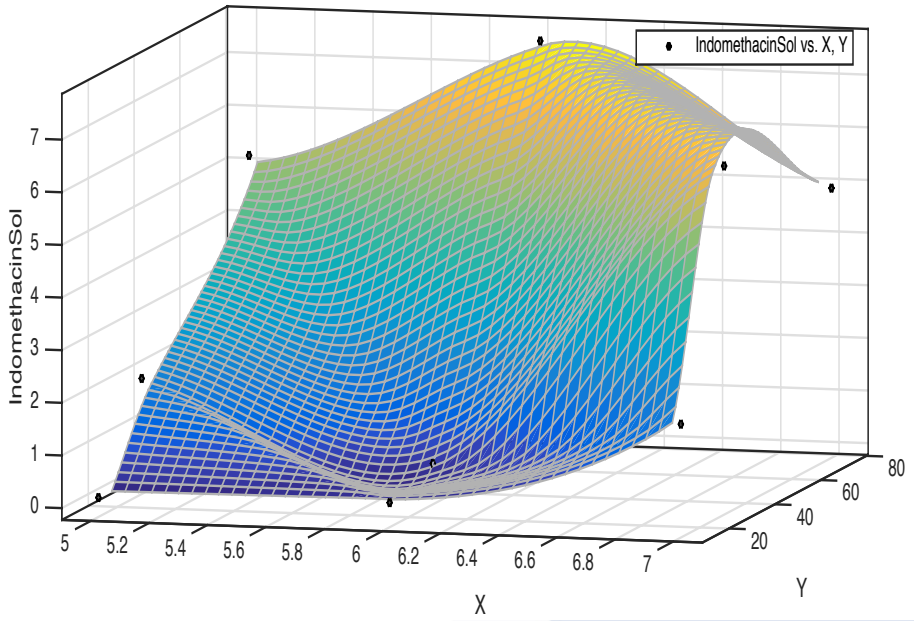
4CMD Matrix

- Indomethacin

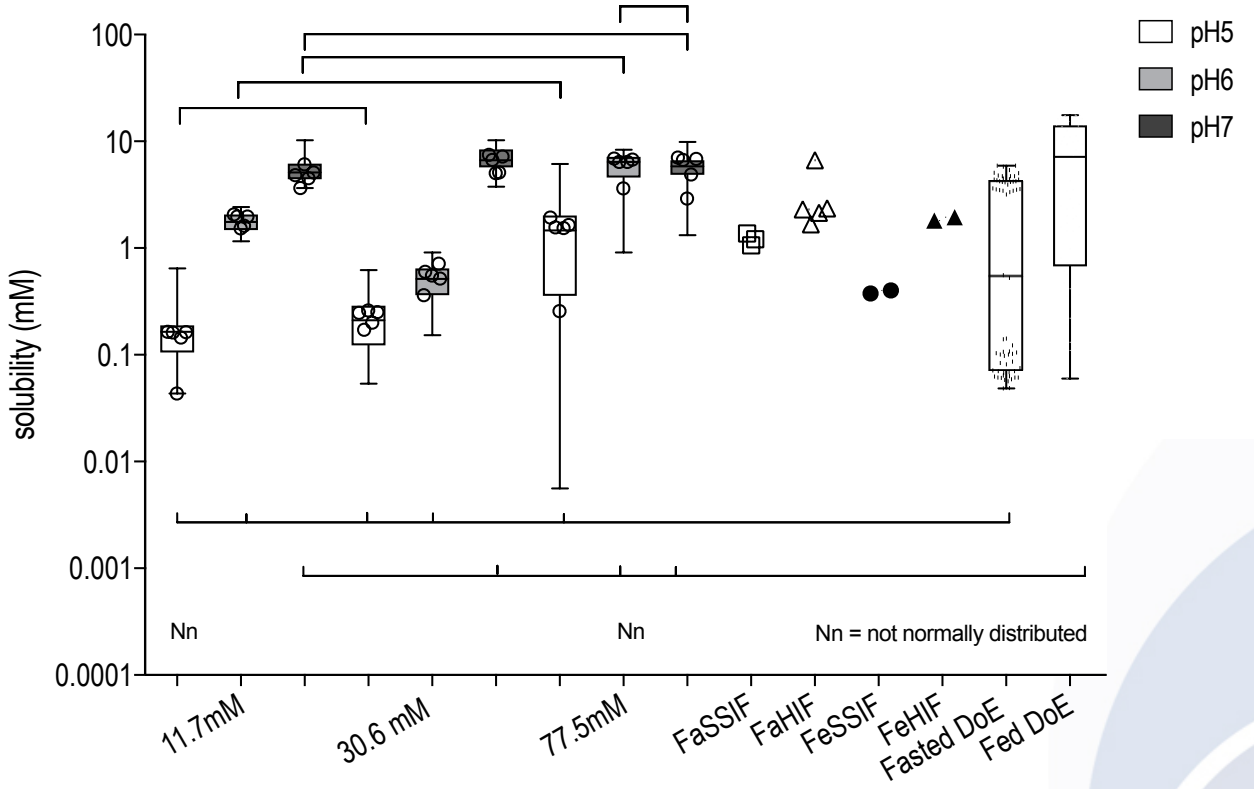




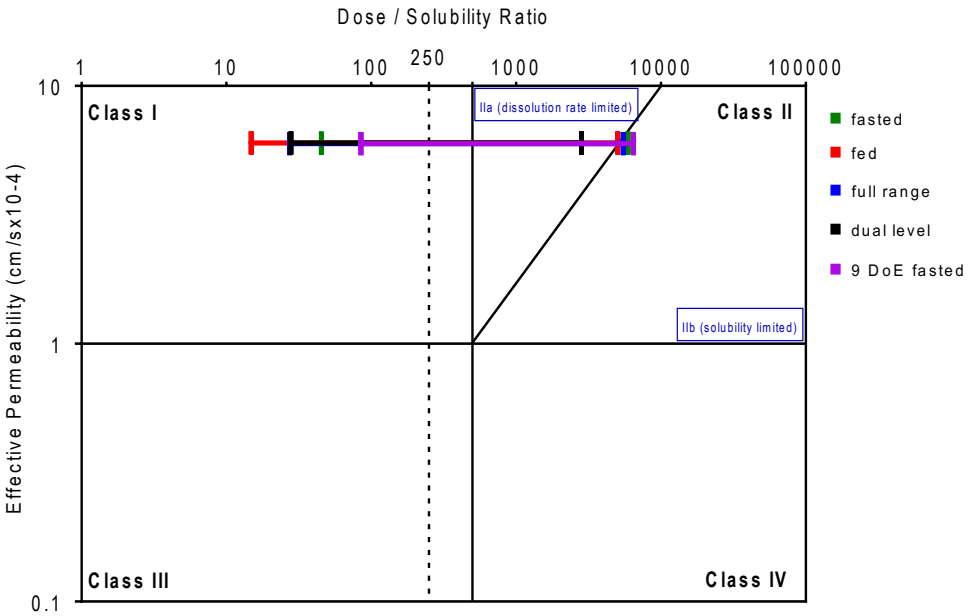
Unpublished Data

Relationship with DoE

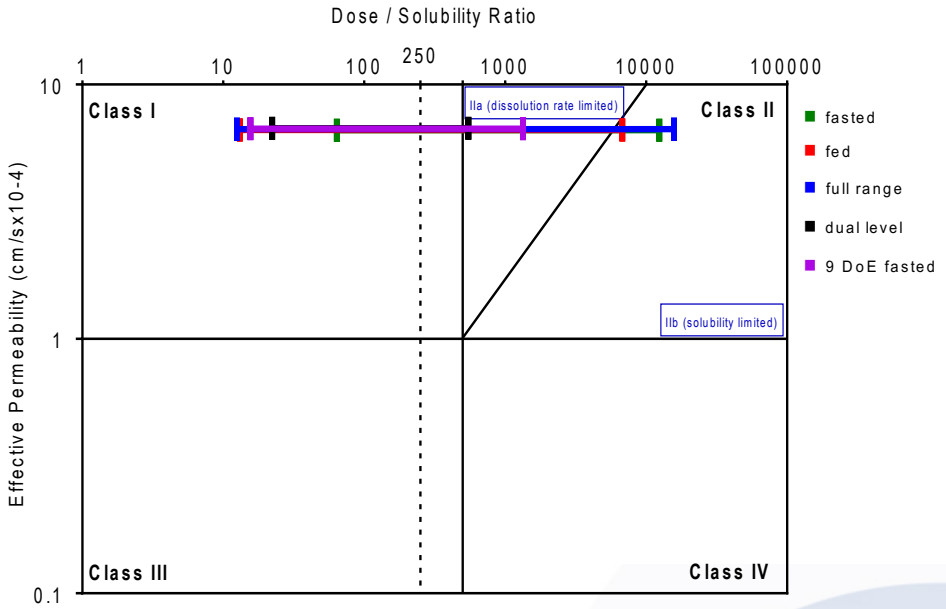
- Indomethacin



Practical Application - BCS & DCS



Indomethacin

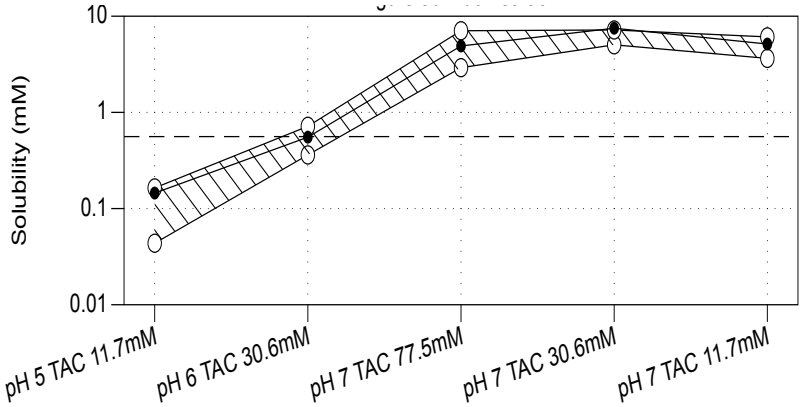


Felodipine

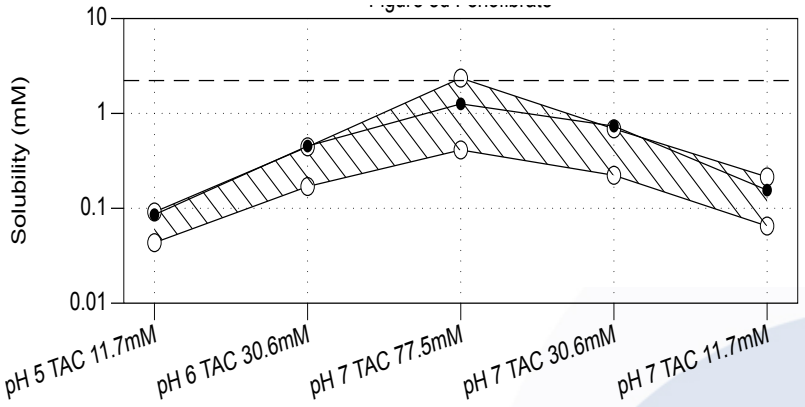
Practical Application - Compartmental Analysis

- 4CMD represents 9 possible intestinal compartments

Indomethacin



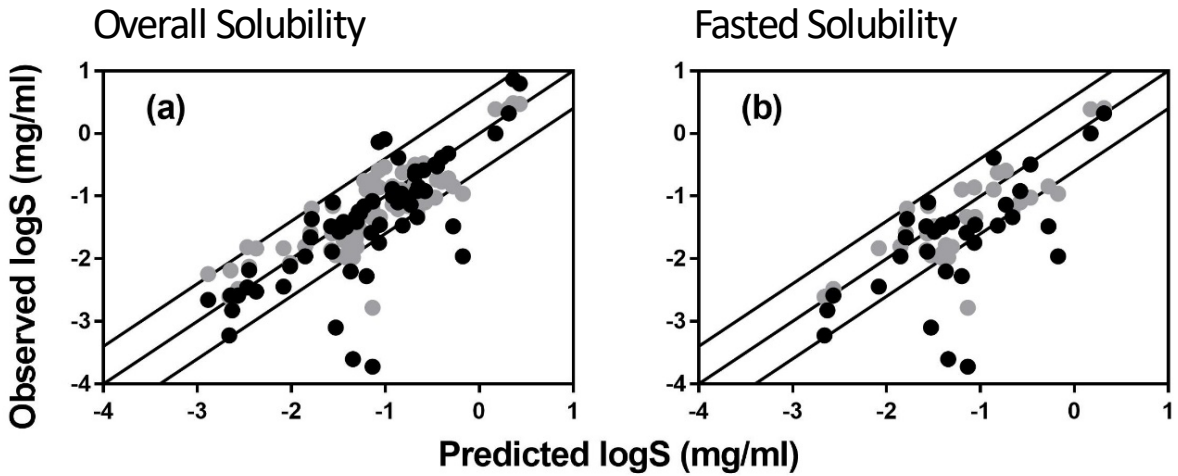
Fenofibrate



Unpublished Data

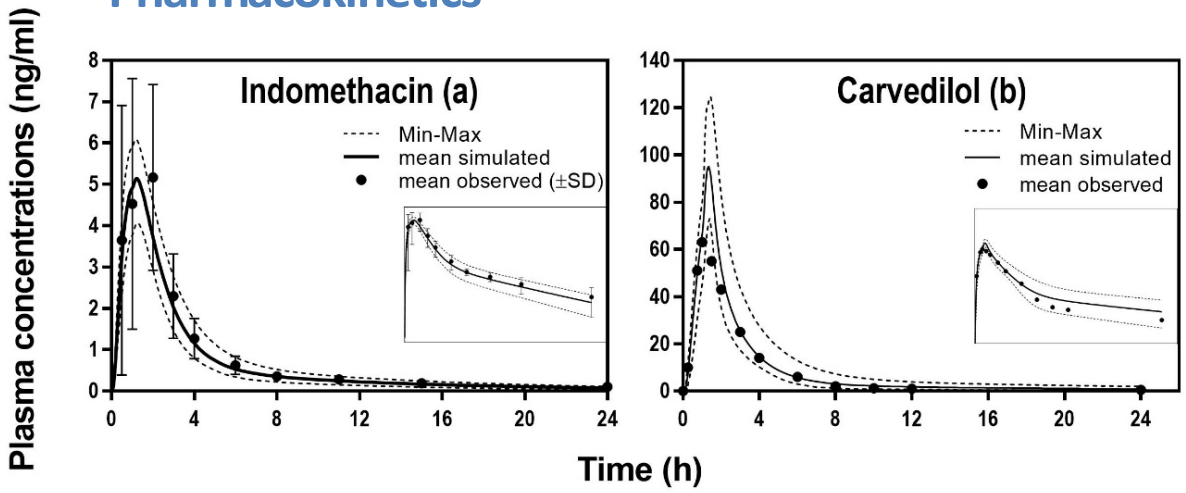
Practical Application – Prediction

Solubility



Pharmacokinetics

Unpublished Data



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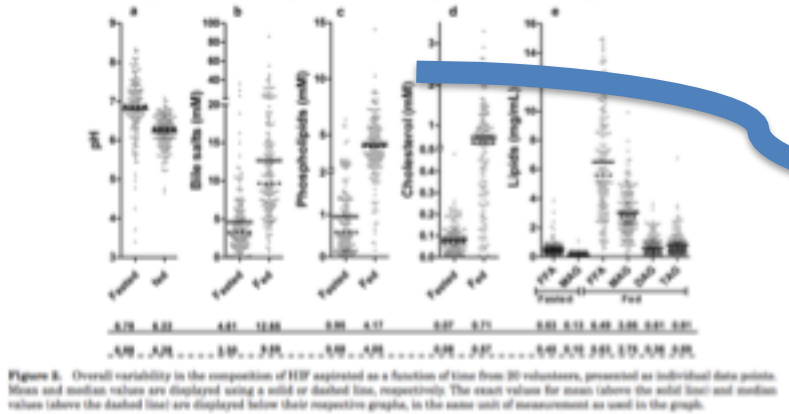
Experimental Caveats – Factor Concentrations

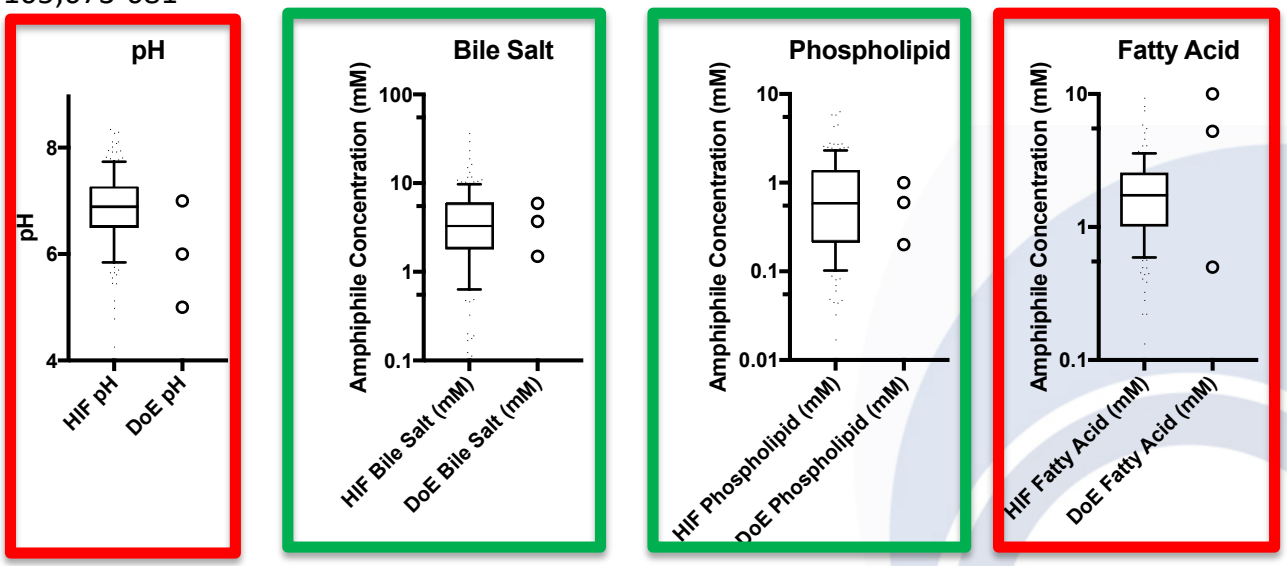


Riethorst, D., et.al., (2015) J.Pharm.Sci., 105;673-681

Cholesterol

Fasted analysis only

X

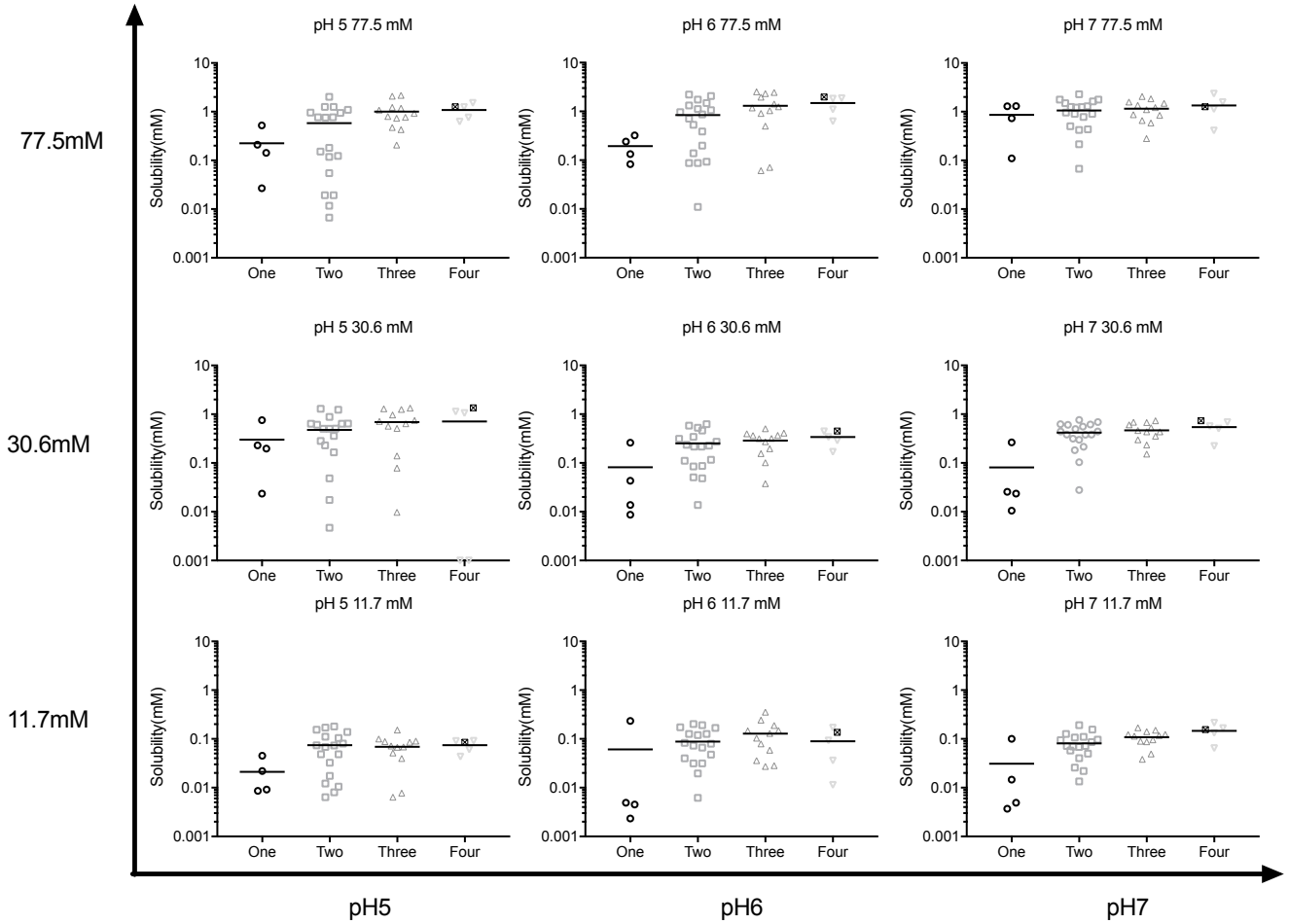


Khadra, I., et.al., (2015) Eur.J.Pharm.Sci., 67; 67-75

Experimental Caveats – Factor Ratios

- 4CMD Amphiphile number & amphiphile ratio

Fenofibrate



Unpublished Data

Conclusions

- Single media composition solubility measurement (SIF or HIF)– limited value
  - Position within topography unknown, variability unknown
- Increase number of measurement points – increased information
  - Big DoE – factor and solubility range information
  - Wee DoE – solubility range – with caveats – limited or no factor information
- Choice of media components – the greater the better – see below
  - Number, Concentration and Ratio – appropriate
- Beware – drug specific behavior

- Improved statistical information – HIF composition and SIF solubility
- Structured solubility behavior is present
- Solubility prediction – looking possible – limited initially

Acknowledgment

- Strathclyde OrBiTo Team
  - Gavin Halbert, Clive Wilson, Ibrahim Khadra, Claire Dunn, Jeremy Perrier, Bayan Ainousah
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- Mr Jeremy Perrier and Gavin Halbert
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- Ms Bayan Ainousah
  - Funded by Saudi Government

Thank you – for listening